EXHIBIT 4

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New York Office
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August 30, 2021

VIA ONLINE & FEDEX

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: *Supplement to Citizen's Petition Associated with Cassava Sciences, Inc. (FDA-2021-P-0930)*

Dear Commissioner Woodcock:

In his recent public comments about the accelerated approval of Biogen's Alzheimer's Disease drug, Dr. Billy Dunn stated that the agency uses "a rigorous, science-based approach" in evaluating drug candidates. If this is true, the FDA has a continuing duty to carefully assess the safety and effective of Simufilam, based on the scientific research relied upon by Cassava Sciences. And this research rises and falls completely on the controversial work of Dr. Hoau-Yan Wang and Dr. Lindsay Burns, the wife of Remi Barbier, the President and CEO of the company.

In my initial petition, I provided extensive documentation regarding my clients many concerns about the accuracy and integrity of Drs. Wang and Burns' clinical and preclinical data supporting the ongoing clinical evaluation of Simufilam, as well as the Company's own clinical data analyses. Due to the numerous serious red flags associated with their foundational research, I formally requested that you halt two ongoing trials of the drug (NCT04388254 and NCT04994483), pending a thorough audit by the FDA of the matters described therein.

Over the last two weeks, publicly and privately, the scientific community has validated many of my clients concerns and identified countless new errors and anomalies that strongly suggest scientific misconduct in their reports about both preclinical and clinical data. To assist your Staff's review of Cassava Sciences' research, we have enclosed a detailed technical document that summarizes the community's troubling findings and a few new ones we have identified. I also have enclosed my correspondence with Dr. Dunn and the other senior FDA officers that were involved in the approval of Simufilam clinical trials and a related press release issued by my law firm.

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In conclusion, in the "For Better Science" blog, it has been recently reported that the City University of New York has commenced an investigation into Dr. Wang's scientific research. In any case, the FDA should quickly follow suit and conduct a rigorous audit of all Cassava Sciences research. While you have 150 days to adjudicate my Citizen's Petition, the need for the FDA to take emergency action couldn't be more urgent. Cassava Sciences has publicly announced that it plans to commence Phase 3 clinical trials of Simufiliam (NCT04994483), with as many as 750 vulnerable Alzheimer's patients, only two days from now.

Respectfully submitted,

Jordan A. Thomas

Enclosures

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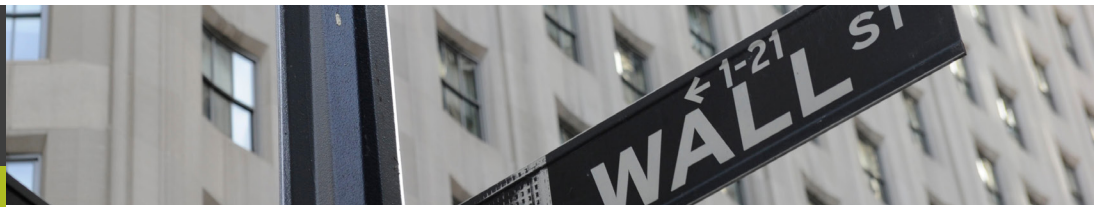

Supplemental Statement of Concern Regarding the Accuracy and Integrity of Clinical and Preclinical Data Supporting the Ongoing Clinical Evaluation of Compound PTI-125, Also Known As Simufilam

Docket #: FDA-2021-P-0930

August 30, 2021

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Supplemental Statement of Concern Regarding the Accuracy and Integrity of Clinical and Preclinical Data Supporting the Ongoing Clinical Evaluation of Compound PTI-125, Also Known as Simufilam

A. Amendments

In my Citizen Petition, specifically our technical summary exhibit (Technical Summary), we noted our concerns about possible data manipulation in both preclinical and clinical studies from Cassava. We believe the **pre-clinical data** concerns we raised **completely undercut the foundational data for a role for filamin A in Alzheimer's disease (AD) and for any efficacy of Simufilam for treating AD.** In this amendment, we wish to re-emphasize our concerns about the **clinical data** and supplement those concerns with new information identified by us and others in the scientific community, since the publication of my petition.

The Company has performed two AD studies with PTI-125/Simufilam: a **phase 2a study** with 13 patients and **a phase 2b** with 64 patients. The Company has disclosed details of these studies on multiple occasions; we focus on five specific instances here:

1. The Company issued a press release on 15 May 2020 (https://www.globenewswire.com/en/news-release/2020/05/15/2034228/8339/en/Top-line-Results-from-a-Phase-2b-Study-of-PTI-125-in-Alzheimer-s-Disease-Does-Not-Meet-Primary-Endpoint.html) in which they announced that for the **phase 2b** trial the "top-line results … did not meet" the Company's primary endpoint. These data focused on analyses **of cerebrospinal fluid (CSF)**.
2. The Company issued a press release on 14 September 2020 announcing "final" results of the **CSF samples in the phase 2b** study (https://www.cassavasciences.com/news-releases/news-release-details/cassava-sciences-announces-final-results-phase-2b-clinical-study). We refer to this second announcement as the "**re-do.**"
3. The Company published **phase 2a** in a scientific manuscript entitled "PTI-125 REDUCES BIOMARKERS OF ALZHEIMER'S DISEASE IN PATIENTS in The Journal of Prevention of

Alzheimer's Disease (2020), authored by Drs. Wang and Burns (and others). We and others **see major red flags in all three disclosures of clinical biomarkers discussed below**.

4. The Company presented at the 2020 Clinical Trials on Alzheimer's Disease meeting (7 November 2020) a presentation entitled "Sumifilam [sic] Significantly Improves Eleven CSF Biomarkers in a Randomized, Placebo-controlled, One-month Clinical Trial in Alzheimer's Disease Patients" (the "**CTAD presentation**").
5. At the 2021 *Alzheimer's Association International Conference* (AAIC) the Company presented new supplemental clinical data from **plasma** samples obtained from the patients in the **phase 2b** study in a poster presentation ("the **Poster**").

For each occasion in which clinical data was disclosed, we outline concerns below and provide new information discovered since the filing of my petition.

A.1. and **A.2.** **<u>Concerns about the Phase 2b clinical trial "re-do".</u>**

In the Technical Summary, we listed our concerns about Company's statements regarding the initial and subsequent analysis of the original Phase 2b data. Specifically, we noted that the Company was not transparent regarding the "re-do" analysis of the Phase 2b data. To reiterate, on 15 May 2020, Cassava reported that PTI-125 did not meet its primary end points, which were a panel of AD biomarkers in cerebrospinal fluid (CSF). However, on 14 September 2020, the Company announced a that reanalysis of these same CSF patient samples showed that Simufilam showed significant improvements across the panel of biomarkers. This press release explained that, "A key objective of this study was to measure changes in levels of CSF biomarkers in study participants before and after 28 days of treatment" and that **"All CSF samples were sent to outside labs for bioanalysis … An academic lab generated final results."** In its 2020 Form 10-K at 12 (20201231 10K (sec.gov), the Company makes a similar statement suggesting the independence of the redo, "With its validity in question, the initial bioanalysis serves no useful purpose. **Backup CSF samples were subsequently sent to a second**

outside lab for bioanalysis. All bioanalyses were conducted under blinded conditions to eliminate any possibility of bias."

Since filing the petition, we found a pre-print on Research Square from the Company describing the biomarker redo (https://www.researchsquare.com/article/rs-249858/v1). This manuscript lists Wang, Burns, Barbier and others from Cassava as authors. Importantly, the Oversight and Settings section states that **"CSF samples were analyzed at City University School of Medicine."** Furthermore, a section entitled "Author Contributions" reads **" Biomarker analyses were conducted blind to treatment and time point by H-YW, ZP and K-CL" referencing Wang and his associates who conducted the CSF sample redo.**

This is a **MAJOR** problem for two reasons. First, Wang is a long-time member of Cassava's Scientific Advisory Board, one of its principal paid scientific consultants and its lead scientist responsible for the Company's Simufilam research, so his secretly conducting the redo contradicts Cassava's key public statements, including the September 2020 press release and 2020 Form 10-K, which stated that the samples were sent to outside labs for bioanalysis. Second, the scientific community has identified countless red flags that call into question the accuracy and integrity of Wang's research. In fact, some scientific integrity experts (see below) have suggested that most of his published research has data that appears to be **"deliberately falsified or fabricated**." Therefore, the phase 2b redo is inconsistent with Cassava public representations (and those likely made to the FDA) and were performed by a widely discredited scientist whose related work includes more than 100 documented red flags, adding new questions regarding the accuracy and integrity of any results reported by the Company.

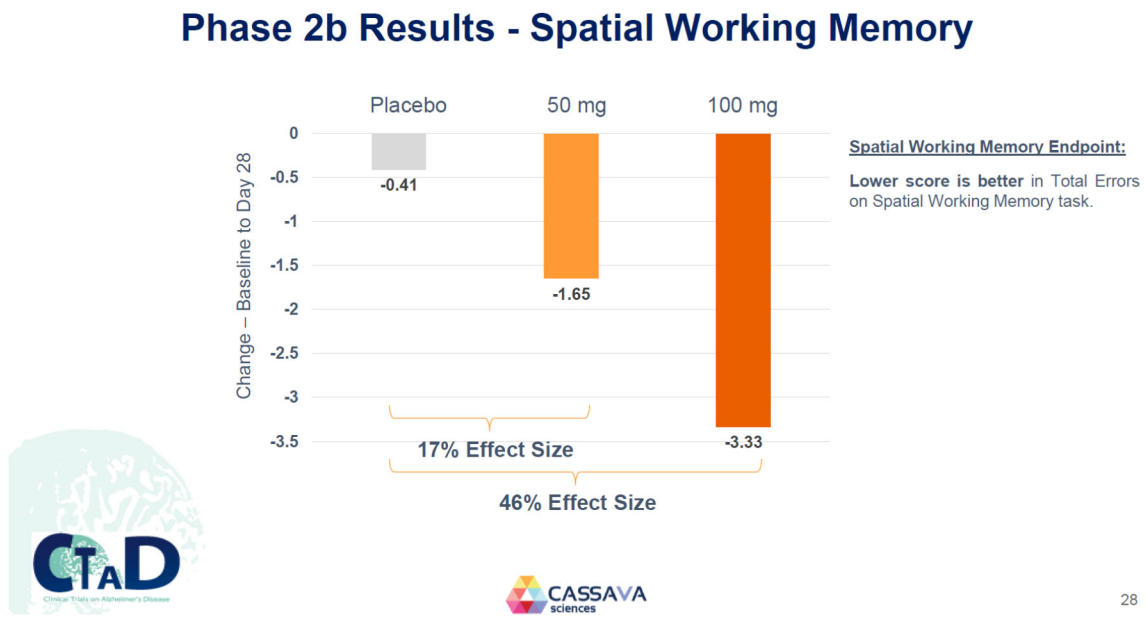
A.3. Concerns About the Phase 2a Clinical Trial.

Our Technical Summary highlighted potential image manipulation in the analysis of the Company's Phase 2a clinical data, which we originally identified in the above referenced 8-K filing of 5 December 2019. We subsequently found that this same image is included in Figure 3A of a scientific

manuscript entitled "PTI-125 REDUCES BIOMARKERS OF ALZHEIMER'S DISEASE IN PATIENTS in The Journal of Prevention of Alzheimer's Disease (2020), authored by Drs. Wang and Burns (and others). Additionally, since dissemination of the Citizen Petition, other scientists have investigated this publication and others. Specifically, Dr. Elisabeth Bik, a former Stanford University scientist and **the world's best-known detective of image manipulation in scientific publications**, confirmed our analysis of this image in a comment on PubPeer. She expressed major concerns with the integrity of these phase 2a data and advised the inspection of the original images is needed to assess the authenticity of the clinical study results. (https://pubpeer.com/publications/A8DD7059A8A7F13D4899049A83F61E). It is important to note that Remi Barbier, Cassava's President and CEO, is listed as an author on this paper. As this was a 2020 paper, the authors should still have all the original high-resolution images for these clinical studies and inspecting the images would confirm or refute our concerns.

A.4. <u>Concerns About Cognitive Data in the CTAD Presentation.</u>

Slide 27 of the CTAD Presentation (available for download at https://www.cassavasciences.com/static-files/5f96b2d4-46e8-4936-a6cf-8332a56f19b1) presents Phase 2b Results from a Spatial Working Memory endpoint and is reproduced below:



The underlying data for these results have been deposited by the Company on ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT04079803?view=results) and do not support the data provided in the CTAD presentation. This initial analysis was provided by Jesse Brodkin on Twitter (https://twitter.com/jesse_brodkin/status/1432131665908928517). The deposited results on ClinicalTrials.gov are provided below:

8. Secondary Outcome

Title	Spatial Working Memory Test
▼ Description	Cognitive assessment of spatial working memory: A number of colored squares (boxes) are shown on the screen. By selecting the boxes and using a process of elimination, the subject should find one yellow 'token' in each of a number of boxes and use them to fill up an empty column on the right-hand side of the screen. The number of boxes is gradually increased to a total of 8 for the subjects to search. The colors and positions of the boxes are changed from trial to trial to discourage stereotyped search strategies.
Time Frame	Day 1 to Day 28

▼ Outcome Measure Data

▼ Analysis Population Description
Removed from analysis were the 3 patients with no detectable drug in plasma, 2 patients with ≥25% non-compliance by pill counts, one patient with no baseline test and one who did not understand instructions per rater notes.

Arm/Group Title	Placebo Cohort	Simufilam (PTI-125), 100 mg Tablets Cohort	Simufilam (PTI-125), 50 mg Tablets Cohort
▼ Arm/Group Description:	Placebo oral tablets administered twice daily (BID)	Simufilam, 100 mg oral tablets administered twice daily (BID)	Simufilam, 50 mg oral tablets administered twice daily (BID)
Overall Number of Participants Analyzed	22	18	17
Mean (Standard Deviation) Unit of Measure: Change from Day 1 in total errors			
	-0.41 (7.54)	-2.31 (7.45)	-3.35 (4.86)

Note that the change from Day 1 in total errors (ClinicalTrials.gov) **does not match** the data in the CTAD presentation. Further, the 50 mg treatment group demonstrated a greater difference than the 100 mg treatment group. An additional concern is that any analysis of change between treatment and placebo appears to be compromised by inequivalent baseline measurements. Also present on ClincalTrials.gov and reproduced below are the **baseline** measurements for the three treatment groups (note that the header is discontinuous with the Spatial Working Memory Data to avoid copying data not relevant to this discussion):

Baseline Characteristics Go to

Arm/Group Title	Placebo Cohort	Simufilam (PTI-125), 100 mg Tablets Cohort	Simufilam (PTI-125), 50 mg Tablets Cohort	Total
Arm/Group Description	Subjects administered matching placebo tablets twice daily for 28 days.	Subjects administered 100 mg simufilam tablets twice daily for 28 days.	Subjects administered 50 mg simufilam tablets twice daily for 28 days.	Total of all reporting groups
Overall Number of Baseline Participants	22	21	21	64
Baseline Analysis Population Description	[Not Specified]			

Spatial Working Memory total errors [1] [2] Mean (Standard Deviation) Unit of measure: Errors					
	Number Analyzed	22 participants	18 participants	17 participants	57 participants
		19.0 (7.49)	22.1 (5.88)	22.3 (6.64)	21.1 (6.67)

[1] Measure Description: A number of colored squares (boxes) are shown on the screen. By selecting the boxes and using a process of elimination, the subject should find one yellow 'token' in each of a number of boxes and use them to fill up an empty column on the right-hand side of the screen. The number of boxes is gradually increased to a total of 8 for the subjects to search. The colors and positions of the boxes are changed from trial to trial to discourage stereotyped search strategies.

[2] Measure Analysis Population Description: Removed from analysis were the 3 patients with no detectable drug in plasma, 2 patients with ≥25% non-compliance by pill counts, one patient with no baseline test and one who did not understand instructions per rater notes

A.5. <u>Concerns About the 26 July Poster at the AAIC.</u>

On p. 5 of the Technical Summary, we noted a concern regarding a point in Figure 5 (spaghetti plot) within the Cassava Sciences poster presented at the Alzheimer's Association International Conference entitled "SavaDx, a Novel Plasma Biomarker to Detect…". This point in the 100 mg Simufilam treatment group appears to show a value that is not represented in Figure 4 from the same poster. Our initial calculations suggested that this point represented a change from baseline (CFB) of ~+235% yet all points in Figure 4 for the 100 mg Simufilam treatment group are <50%, as illustrated in our markup of the Figures on p. 5 of the Technical Summary. Further, we noted that the 100 mg

Simufilam treatment group in Figure 4 contained 17 points yet the same group in Figure 5 contained 18 points. Since our submission and posting of our Citizen Petition to the FDA (https://www.regulations.gov/docket/FDA-2021-P-0930/document, which contained this Figure and explanation), we have received correspondence from Aaron Fletcher of Bio Research, which performed further analyses on the Poster's Figures. Mr. Fletcher confirmed that the point is not represented on Figure 4, but his measurements suggest that the correct calculation should be ~+150%, not ~+235%. We concur.

In addition to the concerns raised in our Technical Summary (and now amended in this document), Mr. Fletcher of Bio Research also communicated to us additional concerns about the data presented in the AAIC poster. Specifically, Mr. Fletcher notes that analysis of the placebo group in the spaghetti plot (Figure 4) reveals that the largest change from baseline is ~+85% yet there is a point at ~+150% in Figure 5. Mr. Fletcher measured all points in the Figures and recalculated the p-values for the group comparisons. If the missing value for the 100 mg treatment group (described above in the Amendment(s) section is inserted, the p-value changes from the Company's reported value of ~0.01 to a **non-significant p-value of 0.08.** They hypothesize that the missing +150% value from the 100 mg group was moved to the placebo group. **When recalculating using paired *t*-tests accounting for that switch, the p-values for the 50 mg and 100 mg treatment groups become larger (0.034 and 0.15, respectively).** Because the study evaluated multiple biomarkers, **neither of these groups would be considered statistically different from placebo** when accounting for multiple comparisons. We include Mr. Fletcher's spreadsheet with a statistical comparison made using estimated original scatter plot data provided in Figure 4 from the poster presentation and statistical comparisons with the changes described above.

In response to the Citizen Petition, the Company issued a press release on 25 August 2021 in which they stated "Cassava Sciences' [Phase 2b] plasma p-tau data in their 26 July Poster at the AAIC

from Alzheimer's patients was generated by Quanterix Corp., an independent company, and presented at the recent *Alzheimer's Association International Conference* …" In response to the Company's 25 August 2021 press release, Quanterix issued a press release on 27 August 2021 stating, "Cassava previously engaged Quanterix' Accelerator laboratory to perform sample testing based on blinded samples provided by Cassava. **Quanterix or its employees did not interpret the test results or prepare the data charts presented by Cassava at the Alzheimer's Association International Conference (AAIC) in July 2021 or otherwise**." Again, Cassava has implied that an external third-party prepared data that was instead analyzed by Cassava, almost certainly by the externally-discredited Dr. Wang.

B. Supplements

Our Technical Summary and our presentation were organized into three primary areas of scientific Concern and six additional suspicious claims incompatible with scientific norms. Here, we provide supplemental information obtained since our petition was filed.

B.1. Primary Concern #1 – the Validity of Clinical Biomarker Data:

Concerns with these clinical trial issues are supplemented above.

B.2. Primary Concern #2 – the Integrity of Western Blot Analyses:

As we noted in the Technical Summary, analysis of published journal manuscripts shows a series of **anomalies that suggest a 15-year pattern of systematic data manipulation and misrepresentation in virtually every publication underlying Cassava's Simufilam claims**. Many of our specific claims have now been independently validated by others, including Dr. Bik, and posted on PubPeer. Specifically, these include a total of 8 papers by Dr. Wang, including 4 papers co-authored with Dr. Burns, noted to have apparent image manipulation. These manuscripts, and the links to comments in PubPeer that detail her specific findings, are:

a. PTI-125 REDUCES BIOMARKERS OF ALZHEIMER'S DISEASE IN PATIENTS in The Journal of Prevention of Alzheimer s Disease (2020) (https://pubpeer.com/publications/A8DD7059A8A7F13D4899049A83F61E), which presents phase 2a clinical data.

b. Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and Gbetagamma signaling in Neuroscience (2005) (https://pubpeer.com/publications/5E71DFFFC843817787A90968A16765O)

c. Prenatal cocaine exposure uncouples mGluR1 from Homer1 and Gq Proteins in PLoS ONE (2014) (https://pubpeer.com/publications/7D632D5EDFCE01EBBB7BDF55A59F36)

d. Reducing amyloid-related Alzheimer's disease pathogenesis by a small molecule targeting filamin A in The Journal of Neuroscience (2012) (https://pubpeer.com/publications/F91E0D22B887598445BB1F908393EE)

e. Cannabinoid-induced tolerance is associated with a CB1 receptor G protein coupling switch that is prevented by ultra-low dose rimonabant in Behavioural Pharmacology (2007) (https://pubpeer.com/publications/5CA0279B6C960FB98610385BB2AE5C)

f. S 24795 limits beta-amyloid-alpha7 nicotinic receptor interaction and reduces Alzheimer's disease-like pathologies in Biological Psychiatry (2010) (https://pubpeer.com/publications/CD34FCE900CAA9CC35B5E4190DCBE5)

g. High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor–Gs Coupling Underlying Opioid Tolerance and Dependence in PLoS ONE (2008) (https://pubpeer.com/publications/0B03A2B682AAAD6A8E9D7C2C49DD22)

h. A model of negative emotional contagion between male-female rat dyads: Effects of voluntary exercise on stress-induced behavior and BDNF-TrkB signaling in Physiology & Behavior (2021)

(https://pubpeer.com/publications/DBE94DCFD3B1DFA8DA0D3337C4AD35)

In addition to confirming the Western blot data manipulations we detailed in the Technical Summary, Dr. Bik noted multiple other Western blot data examples that appeared to show data manipulation. Further, in the 2012 J Neuroscience manuscript entitled "Reducing amyloid-related Alzheimer's disease pathogenesis by a small molecule targeting filamin A", Dr. Bik discovered apparent duplicated histological images (Figure 8A and 8B) that are reported to represent different treatment conditions. Thus, apparently **duplicated histological images (i.e., not just Western blots) represent an additional form of suspected data manipulation by Drs. Wang and Burns.**

Moreover, Dr. Bik specifically addressed the Company's response (press release 25 August 2021) to the Western blot concerns in our Citizen Petition. On Twitter (Aug 25, 2021, https://twitter.com/MicrobiomDigest/status/1430632512057970701?s=20), Dr. Bik wrote: "Whoa. $SAVA / @CassavaSciences response to (legit) allegations that Western blot bands look similar or spliced **raises even more concerns**." Separately, commenting generally on the Western blots in question in her blog (https://scienceintegritydigest.com/2021/08/27/cassava-sciences-of-stocks-and-blots/) on 27 August 2021, Dr. Bik stated "The parts of the response dealing with the problematic Western blots are not very convincing." In Retraction Watch (https://retractionwatch.com/2021/08/26/biotechs-data-supporting-alzheimers-trials-under-scrutiny/), Dr. David Vaux, deputy director of science integrity and ethics at the Australian Walter and Eliza Hall Institute of Medical Research stated: "**It is not conceivable that features in the images (such as apparent duplications) arose due to coincidence (chance) or accident, leaving the only plausible explanation being that the images were deliberately falsified or fabricated**."

B.3. Suspicious Claims

In the Technical Summary, we noted six further aspects of the research by Drs. Wang and Burns that are incompatible with scientific norms and that raise further suspicions. As follow up to our Citizen

petition to the FDA, the scientific community provided strong support for many of our suspicions as follows:

B.3.1 Suspicious Claim #1: Impossibly High Affinity Binding Between PTI 125 and Filamin A: In the Technical Summary, we noted that the *femtomolar* affinity claimed by Cassava for PTI-125 binding to Filamin A is suspiciously high and seemingly implausible. We also noted that no other group has confirmed this remarkable claim. Dr. Bik noted in a PubPeer post on 26 August 2021 (https://pubpeer.com/publications/F91E0D22B887598445BB1F908393EE) regarding the Company's 2012 paper in The Journal of Neuroscience:

> "Could the authors provide some details on the PTI-125 compound, please?
>
> The Introduction states "PTI-125 binds FLNA with 200 femtomolar affinity to disrupt the Aβ-induced FLNA recruitment to α7nAChRs and to reduce Aβ42 signaling. PTI-125 decreases Aβ42 affinity for α7nAChR, dissociating bound Aβ42. Additionally, PTI-125 provides an anti-inflammatory effect by similarly reducing FLNA association with toll-like receptor 4 (TLR4) and preventing cytokine release. "
>
> But there is no reference given. How can other researchers repeat these experiments if there are no details on molecular structure of the Compound Of Interest, or where to buy the chemical, or some previous study? I understand there are patents and stocks involved, but without any details on the Magical Compound it seems this is not a good, reproducible scientific report."

B.3.2 Suspicious Claim #3. 100% of Filamin in Altered Conformation in Alzheimer's Disease and Largely Restored to Correct Conformation by PTI-125: We noted that in the Neurobiology of Aging 2017 55:99-114 paper, the authors present an image in Figure 2A showing that 100% of Filamin A protein by isoelectric focusing shifts in Alzheimer's disease. However, Alzheimer's disease affects a subset of neurons, so we asked how can 100% of Filamin A shift in AD? Also, we noted that isoelectric focusing gels do not "look" like those in their paper. Since our presentation, Dr. Bik has flagged an

isoelectric focusing gel in Neurobiology of Aging 2017 55: 99-114 as having a band that "appears to be surrounded by a rectangle of a different background than the rest of the blot", which suggests it was manipulated confirming our suspicions around the authenticity of Cassava's isoelectric focusing gels (https://pubpeer.com/publications/80DD10169D3C375C5828BC2711A49B).

B.3.3 Suspicious claim 6. PTI-125/Simufilam Blocks the Interaction Between β-amyloid ("Aβ") and α7-Nicotinic Acetylcholine Receptors ("α7nAChR"). We expressed concerns with their experiments using an antibody to β-amyloid including one in The Journal of Neuroscience 2012:32;9773. Since the petition was made public, Dr. Bik noted that a histologic micrograph (microscopic brain tissue picture) in that Wang et al. Journal of Neuroscience paper that was allegedly stained with anti-Aβ42 looks suspiciously similar to a different brain tissue picture that was allegedly stained with an antibody to Neurofilament. She implied that the same brain section was differentially cut and pasted to reflect different experimental treatments and would confirm our suspicions regarding the invalidity of their β-amyloid antibody-based experiments.

See comment 5 in: https://pubpeer.com/publications/F91E0D22B887598445BB1F908393EE

Data points estimated from Figure 4 scatter plot of % change from baseline of serum p-tau on Cassava's 2021 Alzheimer's Association International Conference poster: https://www.cassavasciences.com/static-files/0854aec6-59b3-4e2b-ac20-c32b7c307b08

Treatment	**Placebo**	**50mg**	**100mg**
	150	73	38
	84	29	32
	63	21	13
	62	17	10
	55	-3	8
	45	-19	-9
	37	-24	-12
	27	-24	-18
	28	-29	-19
Statistical comparison made using estimated original scatter plot data provided in Figure 4 on Cassava's 2021 AAIC poster presentation	18	-34	-30
	17	-39	-31
	6	-42	-35
	3	-49	-39
	-1	-52	-40
	-6	-57	-41
	-11		-52
	-28		-63
	-30		
	-36		
	-73		
Average	20.5	-15.4667	-16.9412
Std Dev	49.21542	36.32171	28.93197
Std Error	11.0049	9.378225	7.017033
T test (calculated comparison to Placebo)		0.023141	0.009258
T Test (from Cassava poster)		0.0216	0.0128

Data points estimated from Figure 4 scatter plot of % change from baseline of serum p-tau on Cassava's 2021 Alzheimer's Association International Conference poster: https://www.cassavasciences.com/static-files/0854aec6-59b3-4e2b-ac20-c32b7c307b08

Changes to data were made based on the information presented in the spaghetti plots (Figure 5) as we believe those are likely the most acurate based on the fact that those were not used for statistical analysis in question that was conducted by Cassava

Treatment	Placebo	50mg	100mg
Statistical comparison made by adding +150% data point (green) from 100mg spaghetti plot in Figure 5 into the 100mg scatter plot data. Change in p-value highlighted below in yellow.	150	73	38
	84	29	32
	63	21	13
	62	17	10
	55	-3	8
	45	-19	-9
	37	-24	-12
	27	-24	-18
	28	-29	-19
	18	-34	-30
	17	-39	-31
	6	-42	-35
	3	-49	-39
	-1	-52	-40
	-6	-57	-41
	-11		-52
	-28		-63
	-30		150
	-36		
	-73		
Average	20.5	-15.4667	-7.66667
Std Dev	49.21542	36.32171	48.3334
Std Error	11.0049	9.378225	11.72257
T test (calculated comparison to Placebo)		0.023141	0.084101
T Test (from Cassava poster)		0.0216	0.0128

Treatment	Placebo	50mg	100mg
Statistical comparison made by adding +150% data point (green) from 100mg spaghetti plot into the 100mg scatter plot data AND removing 150% data point (red)from the Placebo group due to its absence from the spaghetti plot in Figure 5.	150	73	38
	84	29	32
	63	21	13
	62	17	10
	55	-3	8
	45	-19	-9
	37	-24	-12
	27	-24	-18
	28	-29	-19
	18	-34	-30
	17	-39	-31
	6	-42	-35
	3	-49	-39
	-1	-52	-40
	-6	-57	-41
	-11		-52
	-28		-63
	-30		150
	-36		
	-73		
Average	13.68421	-15.4667	-7.66667
Std Dev	39.69894	36.32171	48.3334
Std Error	9.107561	9.378225	11.39229
T test (calculated comparison to Placebo)		0.034681	0.150013
T Test (from Cassava poster)		0.0216	0.0128

Thomas, Jordan A.

From: Thomas, Jordan A.
Sent: Saturday, August 28, 2021 5:15 PM
To: 'billy.dunn@fda.hhs.gov'; 'robert.temple@fda.hhs.gov'; 'eric.bastings@fda.hhs.gov'
Cc: Thomas, Jordan A.
Subject: RE: Cassava Sciences, Inc. Whistleblower Submission...

Gentlemen,

In his recent public comments about the accelerated approval of Biogen's Aducanumab drug, Dr. Dunn stated that the FDA uses "a rigorous, science-based approach" in evaluating drug candidates. If this is true, how can the agency possibly permit a Phase 3 clinical trial of Simufilam (PTI-125) with vulnerable Alzheimer's Disease patients, when there have been more than 100 significant red flags recently discovered in the research relied upon by Cassava Sciences and reviewed by your respective teams?

As you know, on 8/18/21, I filed an FDA whistleblower submission with you and a related Citizen's Petition with the Division of Dockets Management. In these filings, I provided extensive documentation regarding my clients many concerns about the accuracy and integrity of clinical and preclinical data supporting the ongoing clinical evaluation of Simufilam. Due to the red flags associated with the foundational research, upon which you approved the drug for clinical trials, as well as additional red flags associated with the phase 2b clinical trial, I formally requested that the current clinical trial be paused, while a rigorous audit is conducted.

Since these filings, as noted in our recent press release, leading international experts on scientific integrity have publicly validated key aspects of our concerns and have critically questioned the Company's response to my petition. For instance, we encouraged you to review this detailed independent analysis by a well-known expert. Privately, members of the medical and scientific community have also helped us to identify new and significant red flags not included in our initial filings. Accordingly, we renew our offer to assist your team in auditing Cassava Sciences' research and reassessing the safety and effectiveness of Simufiliam. In particular, as soon as possible, my clients formally request the opportunity to brief your teams and other FDA personnel on their numerous troubling findings.

The need for the FDA to take immediate action couldn't be more urgent. Cassava Sciences has publicly announced that it plans to commence its Phase 3 clinical trial of Simufiliam (NCT04994483), with as many as 750 patients, in September—only three days from now.

Respectfully,

Labaton Sucharo
Jordan A. Thomas | Partner
140 Broadway, New York, New York 10005
T: (212) 907-0836 | C: (202) 746-9314

From: Thomas, Jordan A.
Sent: Wednesday, August 18, 2021 12:17 PM
To: 'billy.dunn@fda.hhs.gov' <billy.dunn@fda.hhs.gov>; 'robert.temple@fda.hhs.gov' <robert.temple@fda.hhs.gov>; 'eric.bastings@fda.hhs.gov' <eric.bastings@fda.hhs.gov>

Cc: Thomas, Jordan A. <JThomas@labaton.com>
Subject: Cassava Sciences, Inc. Whistleblower Submission...

Gentlemen,

Your offices were directly involved in the approval of several past clinical trials for the drug Simufilam (PTI-125). In fact, according to a recent Cassava Sciences' SEC Form 10-Q, you personally were involved in discussions with the company that led to an agreement on key elements of a future Phase 3 clinical program for the drug. Accordingly, my whistleblower clients would like to report to you their numerous concerns about the accuracy and integrity of clinical and preclinical data supporting the FDA's ongoing evaluation of Simufilam. The attached report demonstrates an unmistakable pattern of errors and anomalies that consistently favor Cassava's hypotheses and is of a sufficient frequency and magnitude to strongly suggest serious scientific misconduct.

Given the many obvious problems with the underlying research, to protect vulnerable Alzheimer patients, the current clinical trial should be paused by the FDA while a rigorous audit of Cassava's research is conducted...

Respectfully submitted,

Labaton Sucharo
Jordan A. Thomas | Partner
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Labaton Sucharow

Rebuttal to 8/25/21 Cassava Sciences Press Release

August 26, 2021 04:50 PM Eastern Daylight Time

WASHINGTON--(BUSINESS WIRE)--On August 18, 2021, Jordan Thomas of Labaton Sucharow filed a Citizen Petition to the FDA on behalf of our clients who collectively have expertise in neuroscience, drug discovery, biochemistry, and finance. They also hold short positions in Cassava stock.

The Company responded on August 25, 2021 to the Citizen Petition with a press release in which they provided a rebuttal to the specific complaints in the Citizen Petition and denied any wrongdoing. Since the issuance of the press release, leading international experts on scientific integrity have independently validated key aspects of the Citizen Petition and have posted comments on PubPeer. On Twitter, they have critically questioned the Company's response.

Notably, commenting generally on the Western blots in question—**those that reportedly form the foundational data for simufilam (PTI-125) as a treatment for Alzheimer's Disease**—to Retraction Watch, David Vaux, deputy director of science integrity and ethics at the Australian Walter and Eliza Hall Institute of Medical Research (WEHI) stated: "It is not conceivable that features in the images (such as apparent duplications) arose due to coincidence (chance) or accident, leaving the only plausible explanation being that the images were deliberately falsified or fabricated."

Contacts

Media Contact:
Profile for Labaton Sucharow
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